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Looking Beyond Reperfusion

Abstract

Acute Myocardial Infarction is thrombotic occlusion of coronary artery and sudden stoppage of blood supply leading to death of heart muscles. The Reperfusion phase of the treatment although promising could salvage at best only 2-4% of the myocardium at 6 months and also carries the risk of reperfusion injury. Despite the best optimal reperfusion therapy, the mortality of AMI still remains 9% at one year and cardiac failure occurs in 11.0%. This appeals us to look beyond reperfusion therapy, repairing or regenerating lost myocardium via cell based therapy, tissue engineering and gene therapy. Efforts are directed towards regenerating myocardium which may revolutionize the treatment of AMI. This not only will decrease the mortality but also improve long term survival and quality of life.

Keywords: Myocardial Infarction; Reperfusion Injury; Myocardial Salvage; Regeneration

Review Article

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VK Shah[1] and KK Shalia[2]*

[1]Interventional Cardiologist, Sir H. N. Reliance Foundation Hospital and Research Centre, Cardiology Department, India
[2]Scientist, Sir H. N. Medical Research Society, Sir H. N. Reliance Foundation Hospital and Research Centre, India

***Corresponding author:** Kavita K Shalia, Research Scientist, Sir H. N. Hospital and Research Centre, Sir H. N Medical Research Society, 4th Floor Court House, L. T. Road, Mumbai, 400 002, India, Email: kavita.shalia@rfhospital.org

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Reperfusion

The root cause of acute myocardial infarction (AMI) was postulated way back in in 1912 by James Herrick who proposed it to be thrombotic occlusion of the coronary artery [1,2]. This hypothesis prioritized thrombolytic agents into the line of treatment which could remove thrombotic occlusion, restore blood supply to myocardium and prevent or limit the extent of myocardial damage. Hume et al in 1958 was the first to propose this treatment of acute MI based on fibrinolysis [3]. By the late 1970s Reimer, Jennings et al. [4,5] laid down, evidence of reperfusion therapy for the treatment of AMI. In their classical experiment a canine model was subjected to coronary occlusion. The myocardial cell death began within 15 minutes of occlusion and proceeded rapidly in a wave front from endocardium to epicardium. On releasing the occlusion within a narrow time frame (<3-6 hrs) myocardial salvage could be achieved. The degree of salvage was inversely proportional to the duration of ischemia and occurred in a reverse wave front from epicardium to endocardium. The extent of necrosis could be modified by changing metabolic demands and varying collateral blood supply as well as the duration of occlusion. Subsequent to this finding, in 1975 Chazov et al. [6] initiated the phase of reperfusion for the patients of AMI wherein thrombi were lysed by infusing streptokinase directly into the blocked coronary arteries [6]. Subsequently it was also demonstrated that timely reperfusion actually salvaged severely ischemic myocardium [7]. The experimental evidence however, of thrombotic occlusion in the coronary artery of AMI patients was obtained in 1980. It was a landmark study conducted by Marcus DeWood and colleagues who performed coronary angiography in the early hours of AMI and found thrombotic occlusion to be present in the coronary arteries in 87% of patients studied within 4 hours of symptom onset [8,9].

A major breakthrough of this journey was by the GISSI investigators [10] in 1986, who in one of the first cardiac mega-trials, demonstrated a reduction in mortality by streptokinase infused intravenously which then set fibrinolysis as routine treatment for AMI. In the absence of thrombolytic therapy, spontaneous perfusion was observed early after ST elevated MI in 15-21 % of patients at 60-90 minutes after study entry. No further increases were observed within the first day. All thrombolytic regimens improved early patency rates although the speed of thrombolysis varied. The Heparin and Aspirin reperfusion therapy (HART, 1990) investigators demonstrated the importance of concomitant heparin for maximising the effect of tPA [11]. The validity of these composite patency rates generated from many studies of varying design and size including ours (1978) [12] was confirmed by a single large GUSTO (1993) angiographic study [13]. The later study showed that the rates of complete (TIMI 3) perfusion at 90 minutes were 54% with accelerated tPA, 29% with streptokinase plus subcutaneous heparin and 31 % with streptokinase and IV heparin. Mortality at 30 days was lowest with TIMI 3 flow [4.4%]; highest 8.9% among those with absent flow and intermediate in those with partial [TIMI 2] flow [7.4%]. GUSTO 1 convincingly demonstrated that the potential of fibrinolytic agents to save myocardium and lives depended primarily on their ability to induce early (90 minutes), complete (TIMI 3 flow) and sustained coronary artery recanalization. The use of fibrinolytic therapy has since been studied extensively in more than 200,000 patients in randomised clinical trials. A pooled analysis of 58 studies (N=14214 angiographic observations) (1994) formed the basis for an overall profile of patency rates of several commonly used reperfusion regimens [14]. Reduced dose of tissue plasminogen activator (tPA) and abciximab in combination improved patency rates further up to 91%. In contrast to varying early patency with different regimens, patency rates at 3-24 hours and beyond were found to be similar. Reocclusion rates were generally higher after fibrin specific therapy than after nonfibrin agents (13%vs 8%) especially in the absence of optimal concurrent IV heparin (1997) [15]. However reperfusion by thrombolysis is an "illusion" created by the imperfect barometer of the static 90 minute angiographic

view of coronary patency. Clinical and experimental data clearly demonstrate a sobering deterioration of benefit derived from coronary recanalization that is not early, nor rapid with incomplete reflow, with critical residual stenosis, decreased tissue level reperfusion, diminished by cyclical patency or frank re-occlusion or possibly negated by reperfusion injury. Relative and absolute contraindications to thrombolytic therapy are also frequently noted e.g. severe hypertension, recent cerebrovascular accident, recent surgery or history of gastrointestinal haemorrhage. Thus appreciation of the limitations of current thrombolytic regimens created a new window of opportunity to enhance the quality of reperfusion therapy for acute MI.

The concept of catheter based reperfusion for STEMI did not truly emerge until Gru¨ntzig's first description [16] of percutaneous transluminal coronary angioplasty (PTCA) followed by pilot experience of Rentrop and colleagues in 1979 with balloon angioplasty to open the occluded infarct artery in 7 patients [17]. Mechanical recanalization by means of primary angioplasty was first used by Meyer et al. [18] and Hartzler et al. [19] Subsequently the field of catheter based reperfusion for STEMI was developed through a series of observations and reports from multiple centres as well as randomised trials and was quickly adopted in hospitals worldwide [20]. The trials of catheter based reperfusion compared with fibrinolysis showed the advantage of angioplasty and stenting over pharmacological therapy, even accounting for delays encountered in transporting the patients to PCI facilities. For many years there has been an active debate as to which reperfusion therapy is better. Cumulatively 23 randomised trials in 7739 patients showed an advantage for primary angioplasty in terms of short term reduction of mortality, reinfarction and stroke [21]. Angioplasty saved 20 more lives /1000 as compared to thrombolytic therapy clearly showing the superiority of the treatment. The vast majority of these patients underwent balloon angioplasty, but in recent years the use of stenting has largely replaced balloon angiolplasty. The 1990s brought the development of novel percutaneous coronary interventions (PCIs), particularly the introduction of coronary stents, initially bare metal and later drug-eluting stents following intracoronary balloon inflation to overcome restenosis. As summarised in pooled data of nine trials for primary stenting, the results were better for reduction of reinfarction and repeat target vessel revascularisation [22]. Primary angioplasty may be the preferred approach in patients with extensive MI who have immediate access to a cardiac catheterisation laboratory with experienced personnel. Patients having 1) contraindication to thrombolytic therapy 2) cardiogenic shock 3) prior coronary bypass surgery or 4) stuttering onset of pain are candidates only for primary angioplasty. Poor candidates are those in whom undue delays in access to catheterisation laboratories facilities would be expected or those with complex coronary artery disease including left main disease or a small MI.

Boersma et al. [23] have shown in a systematic evaluation of fibrinolytic therapy that when applied within the first hour of symptom onset, 65/1000 patients treated were saved as compared to only 29 lives saved when given 3 hours or more after infarct onset. Similar results were seen in the GISSI –I trial [10]. Regrettably, the same studies showed that only a small fraction (3-5%) of patients presented within this golden hour. In contrast, mechanical reperfusion restores flow almost simultaneously with its successful application. Recently, investigators in the stent versus thrombolysis for occluded coronary arteries in patients with AMI (STOP AMI) trial demonstrated that myocardial salvage index was significantly higher for angioplasty than for lysis at any interval from symptom onset and particularly so after the initial 3 hours [24].

Besides early administration of therapy, complete reperfusion (TIMI III) flow in the infarct artery at 90 minutes is also an important predictor of improved outcomes. Even when brisk flow is achieved with lytic therapy, substantial attrition of the benefit occurs because of intermittent patency (25%), reocclusion (13%) and impaired microvascular flow or no Re-flow (23%). This concept of "illusion of reperfusion" reflects our overestimation of the actual rate of complete reperfusion induced by lytic therapy which probably occurs in only 25% of those treated. Because as compared to lytic treatment primary angioplasty is capable of achieving TIMI III flow in at least 15-35 % more patients, it is reasonable to assume that this difference in the patency rates will translate into clinical benefits [25]. In a pooled analysis of 4 PAMI trials Stone et al have shown that mortality at 6 months post angioplasty with TIMI III flow was 2.6 % versus 6.1% with TIMI II flow and 22.2% with TIMI I flow [26]. Further pre angioplasty flow had a significant impact on the ability to achieve successful reperfusion as well as 6 months mortality after angioplasty wherein success rate was 98.1% for TIMI III flow as compared to 91.5% if there was TIMI 0 flow before intervention [27]. This observation becomes very important in considering strategies to facilitate primary angioplasty. Now that we have entered third decade in reperfusion therapy we can expect iterative improvements in all aspects and finally optimal outcomes and reduction in fatality and morbidity and improvement of long term survival of AMI. Table 1 depicts some important landmark trials for Reperfusion Therapy by Thrmobolysis and Angioplasty.

Reperfusion injury

Myocardial reperfusion reduces ischemic cell death but it can also injure the surviving myocardium. In the 1960s, well before the first human reperfusion studies were carried out, Jennings RB et al. [28] and Krug et al. [29] demonstrated impaired reperfusion after release of a temporary coronary occlusion. Kloner RA et al. [30] reported that reperfusion caused microvascular damage with swelling of capillary endothelial cells and of myocytes, leading to what was termed the 'no reflow phenomenon. Areas of no-reflow have been found to be associated with infarct expansion in animals and a high mortality in patients [31]. Myocardial reperfusion is often accompanied by myocardial injury, commonly known as lethal reperfusion injury. Indeed, in 1985, myocardial reperfusion was referred as 'a double-edged sword [32]. During the past decade, three paradoxes have been incriminated as playing a role in lethal myocardial reperfusion injury [33]. (1) The calcium paradox, which raises intracytoplasmic calcium concentration, (2) the oxygen paradox, in which reperfusion raises myocardial pO2, causing the formation of toxic reactive oxidants and (3) the pH paradox, in which a physiologic pH is suddenly restored in the ischemic zone in which the pH had declined. It has been postulated that these paradoxes are involved in opening a channel in the inner mitochondrial membrane, the so-called mitochondrial permeability transition pore, and that the resultant rapid influx of calcium and reactive oxygen species through these pores damages mitochondria, which in turn fail to synthesize high energy phosphate, thereby leading to myocyte death.

Table 1: Some Important Landmark Trials for Reperfusion Therapy.

	Authors/ Trials	Year	Outcome
	Reperfusion by Thrombolysis		
1	Charzov EI et al. [6]	1975	Thrombolysis by Streptokinase in blocked arteries
2	GISSI investigators [10] in	1986	Reduction in mortality by streptokinase infused intravenously
3	The Heparin and Aspirin reperfusion therapy (HART) investigators [11]	1990	The importance of concomitant heparin for maximising the effect of tPA
4	GUSTO (1993) angiographic study [13]	1993	The validity of composite patency rates
5	Granger CB, White HD, Bates ER, et al. [14]. (pooled analysis)	1994	Formed the basis for an overall profile of patency rates of several commonly used reperfusion regimens.
6	Barbagelata NA, Granger CB, Oqueli E, et al. [15]. (pooled analysis)	1997	Reduced dose of tissue plasminogen activator (tPA) and abciximab in combination improved patency rates further up to 91%.
7	Meyer et al. [18]	1982	Mechanical recanalization by means of primary angioplasty first used
8	Hartzler et al. [19]	1983	
9	Hall D, Gruentzig A. [20]	1984	The field of Catheter based Reperfusion for STEMI
10	Keeley EC, Boura JA, Grines CL [21]	2003	Advantage of primary angioplasty over pharmacological therapy

Prevention of lethal myocardial reperfusion injury: The clinical value of ischemic preconditioning local or remote is useful only when the timing of the prolonged ischemia, such as that induced by cardiac surgery or a PCI is known. It is not applicable to patients with the usual AMI in whom the time when the coronary occlusion will occur is of course not known. Many interventions to prevent or diminish lethal myocardial reperfusion injury have been studied [34]. Two are particularly interesting and have shown some promise, both in preclinical studies as well as in small, but intriguing proof of principle clinical trials. The first is an extension of the principle of cardiac preconditioning, in which brief cycles of alternating ischemia and reflow prior to a sustained occlusion reduce the size of the subsequent infarct [35]. It has been observed that this cyclic ischemia can be induced in an organ or tissue other than the heart, yet remain cardioprotective, an intervention termed 'remote ischemic preconditioning [36,37]. However, 'postconditioning' in which the cyclic periods of ischemia and reflow are begun immediately after the prolonged occlusion is relieved - has also been shown to reduce ischemic injury [38] and it too can be effective when carried out remotely [39]. Conditioning can also be begun during the occlusion and it is then referred to as 'perconditioning' [40]. Another technique used to overcome reperfusion injury was "Aspiration thrombectomy prior to coronary stenting" to overcome reperfusion injury. However Salloum et al. [41] during PCI of Saphenous Vein Grafts had demonstrated that in spite of using distal protection devices i.e. filters to capture the insoluble particulate matter, there were soluble factors which may injure the distal microvascular bed. This may explain the additional myocardial injury occurring post reperfusion therapy. A meta-analysis [42] from combined experience from randomized trials suggested that the use of anti-embolic devices did not decrease early mortality or reinfarction during PCI for native vessel AMI. However, in the subsequent years, the TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction) Trial found that aspiration improved myocardial blush scores and ST-segment resolution (STR), and also was associated with lower mortality at 1 year. Compared with conventional PCI, thrombus aspiration before stenting of the infarcted artery seems to improve the 1-year clinical outcome after PCI for ST-elevation myocardial infarction [43]. A Meta-analyses showed improved measures of myocardial reperfusion (TIMI flow, myocardial blush, and STR) and improved procedural outcomes (reduced no-reflow and distal embolization), and three of four trials showed reduced mortality with aspiration thrombectomy which has received a Class IIa indication with primary PCI in the recent ACC/

AHA and ESC Guidelines [44]. Unanswered questions include whether there is truly a mortality benefit with aspiration, which subgroups may and may not benefit from aspiration, and whether patients with large thrombus burden are better treated with mechanical thrombectomy [44]. The second is pharmacologic conditioning, in which cyclosporin A was infused intravenously just prior to balloon inflation. Following encouraging preclinical studies, Griffiths et al. [45] conducted a three-center clinical trial and showed that Cyclosporin A reduced infarct size. The mechanism of protection afforded by Cyclosporin A has been prevention of opening of the mitochondrial permeability transition pore [46]. However, subsequent large randomised trials Cyclosporin and Prognosis in Acute Myocardial Infarction Patients (CIRCUS) [47] and Cyclosporine A in Reperufsed Acute Myocardial Infarction (CYCLE) [48] have failed to show any benefits. Another pharmacological agent was Atrial natriuretic peptide which in animal experimental studies had shown that its prior administration reduced the reperfusion injury through activation of known prosurvival signalling pathways [49]. In a large clinical trial administering Carperitide (an ANP analogue) at a time of PPCI demonstrated 14.7% reduction in enzymatic MI size [50]. Table 2 states trials on prevention of myocardial reperfusion injury. It has been estimated that timely reperfusion can salvage approximately 50% of severely ischemic myocardium [51] and that prevention of lethal myocardial reperfusion injury should prevent the necrosis of an additional 40%. If the latter is successful, it would further substantially reduce the mortality from AMI [33]. Many other trials have been carried out with each modality for reducing reperfusion injury in patients presenting with STEMI [52].

Table 2: Trials on Prevention of Lethal Myocardial Reperfusion Injury.

No.	Authors/ Trials	Year	Outcome
	Brief cycles of alternate ischemia and reflow		
1	Murry CE et al. [35]	1986	Cardiac Preconditioning
2	Hausenloy DJ et al. [36]	2008	Remote ischaemic preconditioning
3	Botker HE et al. [37]	2010	
4	Zhao Z-Q et al. [38]	2003	Post Conditioning-Cardiac
5	Kerendi F et al. [39]	2005	Remote Post Conditioning
6	Sarmento-Leite R [40]	1993	Per-conditioning
	Thrombus aspiration before stenting of the infarcted artery		
5	Vlaar PJ et al. [43]	2008	Compared with conventional PCI, seems to improve the 1-year clinical outcome after PCI for ST-elevation myocardial infarction
6	Brodie BR et al. [44]	2011	Meta-Analysis of 4 trials showed improved measures of myocardial reperfusion (TIMI flow, myocardial blush, and STR) and improved procedural outcomes (reduced no-reflow and distal embolization), and reduced mortality with aspiration thrombectomy
	Pharmacological Conditioning: 1. Cyclopsorin A		
1	Piot C et al. [46]	2008	Cyclosporin A reduced infarct size
2	Cung TT et al. [47]	2015	CIRCUS Trial –failed to show the benefit
3	Ottani F et al. [48]	2016	CYCLE Trial-failed to show the benefit
	Atrial Natriuretic Peptide		
1	Kitakaze M et al. [50]	2007	Reduced reperfusion injury through activation of prosurvival signalling pathways

Salvage of myocardium

The goal of reperfusion therapy is to restore the full nutritive flow and salvage myocardium. However after the introduction of these two modalities of the reperfusion almost 20 years ago, there is very little evidence in the reduction of long term mortality with the current established reperfusion therapies. Rapid reperfusion of the occluded arteries is of great importance in salvaging ischaemic myocardium and limiting the size of infarct. Unfortunately, myocardial necrosis starts rapidly and

the "damage is done" largely before patients reach the hospital and before myocardial reperfusion at the tissue level is achieved. Congestive heart failure is the commonest cause of frequent hospitalisation after MI with 50% of the patients dying within 5 years of diagnosis. Despite optimal pharmacotherapy and mechanical devices, the morbidity and mortality remains high. Left Ventricular (LV) function is the single important determinant factor for improved long term survival after an AMI. Contemporary reperfusion strategies using percutaneous interventions are shown to be associated with only modest improvements in global LV function as evidenced by 2% to 4% increase in the ejection fraction (EF) at six months after an AMI. [24] Cardiac transplant seems to be an ideal option for a vast number of these patients, but due to lack of donor hearts cannot meet even a partial demand of it. Other measures like heart assist devices and pacemakers have shown not to prolong the survival and are not cost effective. Various strategies like thrombectomies and distal protection devices have been tried to improve the microvascular dysfunction that occurs after the reperfusion of myocardium but have failed to salvage the myocardium [41]. A host of pharmacotherapies have failed miserably except perhaps high dose adenosine, the story for which is not completely closed. Other modalities like COOl MI, HOT MI, APEX MI and post-conditioning of MI [42,53], have not held any promise as shown by the studies. Given the less than ideal results of salvaging ischemic myocardium so far, recently a great interest has emerged in myocardial regeneration therapy.

Regeneration of myocardium

The dogma that the heart is a terminally differentiated organ incapable of self renewal has been challenged. Although the cells derived from resident cardiomyocytes or circulating cells have regenerating capacity, their ability to minimize the deleterious effects of ventricular myocardial remodelling is limited. The surviving cardiomyocytes bordering the infarct zone becomes hypertrophied as part of adaptive mechanism to compensate for the loss of myocardium. However the normal angiogenesis after the myocardial infarction is insufficient to meet the greater demands for oxygen and nutrients to prevent the apoptosis of the hypertrophied cardiomyocytes. Therefore increasing the perfusion to infarcted myocardium to enhance oxygen and nutrients through the formation of new vessels has the potential to improve the cardiac function. Thus reversal of heart failure would require not only restoration of blood supply but also replacement of myocytes. This can be achieved collectively by stem cells which will increase neoangiogenesis and also replace the lost cardiomyocytes by transdifferentiation. Since early reports in experimental models less than 10 years ago [54-59], the stem cell field has made enormous advances in moving towards clinically applicable treatment options, and we are now at the dawn of a new era. These positive results gave way to clinical trials on human beings wherein transplantation of bone marrow cells (BMCs) into the target coronary artery was carried out [60-63]. The results from small clinical studies suggest that therapy with adult bone marrow derived cells reduces infarct size and improves left ventricular functions and perfusion. An extensive meta analysis by Abdel Latiff A et al. [64] on eighteen eligible studies (N=999 patients) involving adult bone marrow cells such as bone marrow nuclear cells, bone marrow mesenchymal cells and bone marrow derived circulating progenitor cells measuring the same outcomes, demonstrated that as compared to controls, bone marrow transplantation improved left ventricular ejection fraction (LVEF) (pooled difference of 3.66%; 95% confidence interval [CI], 1.93% to 5.4%, P<0.001); reduced infarct scar size (-5.49%; 95%CI: -9.1% to -1.8%; P=0.003); and reduced left ventricular end-systolic volume (LVESV) (-4.8%ml; 95% CI-8.2 to -1.41ml; P=0.006). Further steps required were to carry out multi-centeric randomized large trials targeted to address the impact of intracoronary cell therapy on important outcomes and long term event free survival as compared to the conventional therapy. With this aim Leistener et al. [65] in one of the TOPCARE interim reports and Moccetti et al. [66] in a single-center, open-labelled study have reported that the improvement seen at 6 months in LV functions in ABMSC group was sustained at 24 months including our report [67]. An analysis of 48 eligible randomized controlled trials (enrolling 2602 patients), since August 2014 have demonstrated that as compared with standard therapy, BMC transplantation improved LV ejection fraction (2.92%; 95% CI, 1.91-3.92; P<0.00001), reduced infarct size (-2.25%; 95% CI, -3.55 to -0.95; P=0.0007) and LV end-systolic volume (-6.37 mL; 95% CI, -8.95 to -3.80; P<0.00001), and tended to reduce LV end-diastolic volume (-2.26 mL; 95% CI, -4.59 to 0.07; P=0.06). Early (<48 hours) BMC injection after myocardial Infarction was more effective in reducing infarct size, whereas BMC injection between 3 and 10 days proved superior toward improving systolic function. A minimum of 50 million BMCs seemed to be necessary, with limited additional benefits seen with increasing cell numbers. BMC therapy was safe and improved clinical outcomes, including all-cause mortality, recurrent myocardial Infarction, ventricular arrhythmia, and cerebrovascular accident during follow-up, albeit with differences between acute myocardial Infarction and chronic ischemic heart disease subgroups [68]. MSCs are considered as the most suitable candidates for cardiac cell therapy. MSCs transplantation in the myocardium after ischemic injury has been shown to be cardioprotective in animal models and clinical trials. However, the beneficial effects of MSC in humans are limited because of both poor survival and impaired function of the cells in ischemic tissue. To address these issues, a number of approaches to the modification of MSCs with the aim to improve their survival and proliferation, to reduce the immune reaction, enhance transdifferentiation, and optimize the profile of secreted paracrine factors have been tested [69]. It has been demonstrated that Wharton's jelly-derived mesenchymal stem cells (WJMSCs), a primitive stromal population, could integrate into ischemic cardiac tissues and significantly improve heart function [70,71]. The discovery of adult cardiac stem cells (CSCs) and their potential to restore functional cardiac tissue has fuelled unprecedented interest in recent years. Over the last decade, several independent laboratories have demonstrated the utility of c-kit-positive, lineage-negative cardiac stem cells (c-kit+/Lin- resident CSCs) in alleviating left ventricular dysfunction and remodeling in animal models of acute and chronic myocardial infarction [72]. The first clinical trial of autologous CSCs for treatment of heart failure resulting from ischemic heart disease (Stem Cell Infusion in

Patients with Ischemic cardiOmyopathy [SCIPIO]) phase I trial demonstrated no adverse effects attributable to the CSC treatment, improvement in ejection fraction at 1 year (+13.7 absolute units versus baseline) and 30.2 % reduction in infarct size, significant improvement in the New York Heart Association (NYHA) functional class and in the quality of life, as measured by the Minnesota Living with Heart failure Questionnaire [73]. Another cell types have been, cardiosphere-derived cells (CDCs) as a candidate cell type for regenerative therapy post-MI. These heart-derived cells are stem cells in that they exhibit multilineage potential and clonogenicity, but they work primarily through indirect mechanisms [74]. CDCs were first used clinically in prospective, randomized, controlled CADUCEUS (CArdiosphere-Derived aUtologous stem CElls to reverse ventricUlar dySfunction) trial [75]. Autologous CDCs grown from endomyocardial biopsy specimens were infused via the intracoronary route in 17 patients with left ventricular dysfunction 1.5 to 3 months after MI. Intracoronary administration of autologous CDCs did not raise significant safety concerns. Preliminary indications of bioactivity include decreased scar size, increased viable myocardium, and improved regional function of infarcted myocardium at 1 year post-treatment. These results, which are consistent with therapeutic regeneration, merit further investigation in future trials. Thus, cell-based clinical trials to treat MI have focused on cells derived from the bone marrow or those potentially possessing functional similarities such as cardiac progenitors isolated from heart biopsies. Any benefits provided by these cells in improving heart function, left ventricular ejection fraction, or extending life expectancy after MI have been credited mostly to paracrine effects. Functional restoration of damaged myocardium will require functional cell type with similar phenotype and characteristics of the damaged tissue that can also integrate, survive, and electrically couple to the host. Human pluripotent stem cells (hPSCs) have the ability to differentiate into multiple cell types of the adult body. hPSC-derived cardiomyocytes represent a promising target population for cell-based therapies for MI because they are scalable and the product can be defined with a specific set of release criteria [76,77]. Pluripotent stem cell-derived cardiomyocyte-based therapies have enormous potential to revolutionize the management of heart disease; expedient but careful development is needed to ensure that this potential is fully realized. [78] Cardiac regenerative medicine is promising, and a number of clinical trials in humans have already shown its indisputable safety. However, many factors remain unresolved, such as cell type (bone marrow, adipose tissue-derived progenitors, induced pluripotent (iPS) cells, cardiac resident progenitors, or embryonic stem cells), stimulation of endogenous regeneration through direct reprogramming of fibroblasts into cardiomyocytes, activation of resident cardiac stem cells or induction of native resident cardiomyocytes to re-enter the cell cycle, the route of administration (intramyocardial, transendocardial, or intracoronary), and the time of optimal delivery after MI. All these strategies need to be optimized since their efficiency is low. Several multi-centre trials are on-going in an attempt to answer some of these questions and to prove true benefit in clinical and functional parameters [79]. For the time of optimal delivery, a meta-analysis of trials using multiple timing of BMCs therapy revealed that 4-7 days following AMI ranked better than other timing groups for improvement in LVEF or reduction of the incidence of major adverse cardiac events [80]. The limited survival and engraftment of transplanted cells due to a hostile ischemic environment is a major factor affecting its utilization. Within this environment, the majority of transplanted cells undergo apoptosis prior to participating in lineage differentiation and cellular integration. Therefore, in order to maximize the clinical utility of stem/progenitor cells, strategies must be employed to increase their adhesion, retention, and engraftment in vivo. However, preconditioning of cells or cell manipulations strategies and biomaterials can enhance stem cell survival and engraftment after transplantation. Thus, tissue engineering is also emerging as an option for cardiac regeneration. Biomaterials can incorporate or mimic extracellular function (ECM) function and enhance survival or differentiation of transplanted cells, in vivo. Biomaterials can also promote angiogenesis, enhance engraftment and differentiation, and accelerate electromechanical integration of transplanted stem cells. However, the challenges are enormous, including, selection of the optimal cell source, developing engineered matrices (biological or non-biological; biocompatible or not), establishing the cellular electromechanical coupling, promoting an efficient and stable contractile function, and ensuring functional vascularization [81]. A majority of these experimental processes have only been tested in small animal models. The transposition of a fat flap over the ischemic myocardium has recently been proposed, with promising results in the swine preclinical model of MI [82]. Tissue-engineered, hydrogel-based Mesenchymal stem cells (MSCs) [83] and endothelial progenitor cell [84] therapy have been shown some promising results in re-vascularizing the ischemic myocardium and preserving ventricular function through paracrine effects [85]. Table 3 presents recent cell based clinical trials for cell based therapies of regeneration of myocardium. A new avenue being explored is gene therapy, an emerging multidisciplinary field that identifies key signalling pathways, and creates new technologies and novel vector constructs [86]. Different routes of administration and viral vectors have been tested in small and large animal models with encouraging results [87,88]. Preliminary clinical trials have been conducted for delivering AAV1- SERCA2 [89] or AD-HGF [90] through intracoronary infusion, and have reported benefits in patients with severe heart failure.

Conclusion

While current strategies are not enough to salvage the myocardium physicians will have to come out of their mind set of restricting their use to reperfusion modalities and increased use of antithrombotic, anticoagulants and devices to improve the salvage of myocardium. They have to revolutionary think about newer ways which has been elusive in the last twenty years. Every attempt must be made to optimize reperfusion, prevent reperfusion injuries and work on various fronts for regenerating the new myocardium.

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Table 3: Recent Cell Based Clinical Trials for Cell based therapies for Regeneration of Myocardium.

No.	Authors/ Trials	Year	Type of Cells	Outcome
1	Leistner DM et al. [65]	2011	circulating (CPC) or bone marrow-derived progenitor cells (BMC)	TOPCARE-AMI -5 year follow-up favourable effects on LV function
2	Moccetti T et al. [66]	2012	Bone marrow derived mononuclear cells (BM-MNC)	Stem Cell Transplantation in Ischaemic Myocardium Study-5 year follow-up- sustained improvement of left ventricular function
3	Shah VK et al. [67]	2014	BM-MNC	2 Year Follow-up, better clinical course in stem cell therapy group as compared to patients without this therapy at 24 months follow-up.
6	Afzal MR et al. [68]	2015	An analysis of 48 eligible randomized controlled trials (enrolling 2602) of BMC transplantation patients),	BMC therapy was safe and improved clinical outcomes, including all-cause mortality, recurrent myocardial Infarction, ventricular arrhythmia, and cerebrovascular accident during follow-up, albeit with differences between acute myocardial Infarction and chronic ischemic heart disease subgroups
4	Bolli R et al. [73] SCIPIO Trial	2011	Cardiac Stem Cells	Improvement in ejection fraction and reduction in infarct size
5	Malliaras K et al. (CADUCEUS) [75]	2014	Cardiosphere-derived cells	Decreased scar size, increased viable myocardium, and improved regional function of infarcted myocardium at 1 year post-treatment.

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